A NON-INVASIVE PROSPECTIVE APPROACH FOR THE DETECTION OF ALZHEIMER'S DISEASE

Prashant Kumar
Roll no. 213BM1008

Department of Biotechnology and Medical Engineering
National Institute of Technology, Rourkela
Rourkela, Odisha, India
June, 2015

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Thesis submitted in partial fulfillment of the requirements for the degree of

Master of Technology

in

Biomedical Engineering

by

Prashant Kumar
Roll no. 213BM1008

under the guidance of

Prof.Subhankar Paul

Department of Biotechnology and Medical Engineering
National Institute of Technology, Rourkela
Rourkela, Odisha, India
June, 2015

dedicated to my parents...

National Institute of Technology
Rourkela

CERTIFICATE

This is to certify that the work in the thesis entitled **"A NON-INVASIVE PROSPECTIVE APPROACH FOR THE DETECTION OF ALZHEIMER'S DISEASE"** submitted by ***Prashant Kumar*** is a record of an original research work carried out by him under my supervision and guidance in partial fulfillment of the requirements for the award of the degree of Master of Technology in Biotechnology and Medical Engineering (Biomedical Engineering), National Institute of Technology, Rourkela. Neither this thesis nor any part of it, to the best of my knowledge, has been submitted for any degree or academic award elsewhere.

Prof. Subhankar Paul
Associate Professor
Department of BM/BT
National Institute of Technology
Rourkela

National Institute of Technology
Rourkela

DECLARATION

I certify that

1. The work contained in the thesis is original and has been done by myself under the supervision of my supervisor.
2. The work has not been submitted to any other Institute for any degree or diploma.
3. I have followed the guidelines provided by the Institute in writing the thesis.
4. Whenever I have used materials (data, theoretical analysis, and text) from other sources, I have given due credit to them by citing them in the text of the thesis and giving their details in the references.
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Prashant Kumar

Acknowledgement

This work is one of the most important achievements of my career. Completion of my project would not have been possible without the help of many people, who have constantly helped me with their full support for which I am highly thankful to them.

First of all, I would like to express my gratitude to my supervisor **Prof. Subhankar Paul**, who has been the guiding force behind this work. I want to thank him for giving me the opportunity to work under him. He is not only a good Professor with deep vision but also a very kind person. I consider it my good fortune to have got an opportunity to work with such a wonderful person.

I am also very obliged to **Prof. Krishna Parmanik**, HOD, Department of Biotechnology and Medical Engineering for creating an environment of study and research. I am also thankful to Prof. K. pal, Prof. Amit Vishwas, Prof. A. Thirugnanam and Prof. B. P. Nayak for helping me how to learn. They have been great sources of inspiration.

I would like to thank all faculty members and staff of the BT/BM Department for their sympathetic cooperation. I would also like to make a special mention of the selfless support and guidance I received from PhD Scholar Mr. Dependra Kumar Ban and Mr. Shailendra Kumar Mahanta during my project work.

When I look back at my accomplishments in life, I can see a clear trace of my family's concerns and devotion everywhere. My dearest mother, whom I owe everything I have achieved and whatever I have become; my father, who always believed in me and inspired me to dream big even at the toughest moments of my life.

Prashant Kumar

Abstract

We proposed an automated novel method to detect Alzheimer disease (AD). The methodology involves the analysis of normal and AD MRI (Magnetic Resonance Imaging) brain scans, we extracted some specific portions of brain which changes in case of diseased subjects such as Hippocampus, Septum Pellucidum, fornix and some portion of thalamus. We measured the area of brain parts lost due to AD and compared these measurements with the same aged normal subjects. In this research work various pattern recognition techniques were used that separates the AD brain scans form the brain scans of healthy controlled subjects. These pattern recognition techniques includes segmentation of brain images, wavelet based texture features extraction for the classification of brain scans. We used two different classifiers ANN (Artificial Neural Network) and SVM (Support Vector Machine) and which showed the comparable accuracy, execution time than other classifiers reported so far.

Keywords: Magnetic Resonance Imaging, Image Segmentation, feature extraction, ANN, SVM etc..

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Introduction

Chapter 1

INTRODUCTION

1.1 Overview

It was an old convention that the knowledge, perception, wisdom come with age. Science doesnt agree completely with this statement. It has an evidence that demonstrates the diminution of cognitive function as we grow older after a particular age limit. This kind of cognitive aging include a decline in the rate of performing mental operation such as receiving and capturing information. Searching words and recalling names of the friend, family and places that creates problems for the aged people, as well as recalling details associated with their past events (Gamberini et al., 2006) the ability of sensory organs (for e.g., eye and ear) which are the rudimentary to cognitive function, appear to decay, concentration towards work and learning skills goes down (Park, 2000).

1.2 Alzheimers Disease

Sometimes declination in cognitive function does not happen normally. Faster and more serious declination in numerous cognitive ability found in dementia, which is a typical clinical disorder among elderly individuals. As the count of the old aged person increases then automatically the count of people suffering from memory related disease called dementia increases, which makes various demands on our society in terms of providing facilities for needy persons. The most common cause of dementia is Alzheimers disease (Tabert et al., 2002) that influences the behaviour of individuals, nature and social skills. The name of the disease Alzheimer was taken from name of the German psychiatrist and pathologist Alois Alzheimer after he analysed a female patient in post-mortem in year of 1906. She died at the age of 51. She was suffering from memory problems, pandemonium and problems in analysing simple questions. Alzheimer found two unusual changes in the brain of that lady patient. First highly dense

amount of protein settled outside and between the nerve cells. Second thing he observed that there are some damaged nerve fibres, inside the nerve cells, he also found that the nerve fibre present the brain of the that lady patient was untidy instead of being straight. These information have been used to identify AD. The rate of increment of AD increases with age, when an individual suffering from AD crosses the age of 65, chances of AD enhanced approximately by two times (Minati et al., 2009).

A part from that AD patients are the great responsibility for their relative and caretakers. The clinical diagnosis of AD is characterized by continuation of memory loss and decrement of cognitive abilities.AD starts with precise, terribly, recognized frailty of memory. Further symptoms include indecision, anxiety, moodiness, impulsivity. Pathology of AD is characterized by existence of plaques that is made up of beta amyloid protein also known as amyloid- () peptide and neuro fibrillary tangles that contain tau protein (Hardy and Selkoe, 2002).

The amyloid and tau protein is considered as the primary inducer of the AD in human brain. Another neuropathological features comprise cortical atrophy, hippocampal atrophy, degradation of basal forebrain neurons and the ventricles. In addition, the semantic memory is also affected in case of AD patients. The role of semantic memory is one of the most deceiving factor for exchanging information, messages and in language processing. The shortfall of language processing also indicates initial phase of AD (Kremin et al., 1994). The most damaged area of language appears to be pragmatics and semantics, on the other hand syntax and phonology are comparatively completely conserved (Balota and Duchek, 1991). There is a task to check semantic fluency, in which a patient is asked to form words for a specific semantic class (e.g., birds) in a fixed interval of time, this method is widely used by neuropsychologists to determine retrival of words from semantic memory. The job of the patients is considered to be a quite simple, quick and tactful clinical task that produce very helpful information about the proper functioning of semantic performance and the level of semantic memory (Collette et al., 1999).

The patients performance is usually examined by calculating true responses and errors made by him such as repetition of words and contravention of categories. It appears that the patient apply the simple strategy to perform the job that the patient used the same semantic word number of times (e.g., birds) and moving to another sub category (e.g., fish, animals, etc.) (Troyer et al., 1997). It indicates that the AD subjects are unable to accomplish the task in a way the elderly normal patient do. The semantic fluency test of AD subjects is characterized by depletion in word production and large number of errors made by the patients. If the symptoms of AD continues, it causes severe dementia and patient may die after few years.

There are many diagnosis test through which we can find out that whether the subject is normal or suffering from AD. Some of the diagnosis tests are clinical diagnosis, laboratory tests,

neuropsychological tests, imaging studies (e.g., CT scan or computer tomography, MRI magnetic resonance imaging, PET positron emission topography, SPECT single photon computer tomography), as well as neurophysiological tests (EEG) (Pekkala, 2004). In case of AD patients, during his entire life time, a brain biopsy may encourage the probable detection of AD, but the actual detection of AD is done on the basis of neuropathological findings of autopsy (Van Deerlin et al., 2010).

AD varies with age, as the age increases it gets worse. Its an unrepairable disease with a slow and continuous progression (Pekkala, 2004). The most eminent property is the accelerating dementia. AD results shows memory loss, change in behaviour and changes in personality and decrement in intellectual, social, professional and everyday function of life. There are many types of AD, some of them are known as prehensile AD (patients below the age of 66 falls in this category) and senile AD (patients above the age of 65 falls in this category), but now both the types of AD considered as same AD.

The rate of enhancement of disease vary patient to patient. Generally the clear symptoms of AD is usually appear in the patients between the age of 60 to 70. But between the age of 70-80 AD is generally diagnosed (Rademakers et al., 2003). After the diagnosis of AD, the life expectancy of the individual is approximately 10 years but it may vary from 3 to 15 years depending upon the patients environment, patients diet, his daily life work and the their surroundings (Feldman et al., 2009).

The number of people diagnosed with AD at any time is apprised to be 0.5 % of total population below the age of 65 years, 1% of total number of people between the age of 65-70 years, 30% in individuals above the age of 85 years. In Europe it was estimated that 84% of total people above the age of 65 years diagnosed with AD, the quantity is a bit lesser in young people and larger in ladies if compared to male patients. 65-70% of the dementia patients suffering due to AD. The other cause of dementia in 15-20% cases, patients suffering from several other neural disease such as frontotemporal dementia, Lewys body, picks disease, Hakolas disease, Parkinson disease and Creutzfeldt-Jacob disease. Irregularity in cerebral blood flow, brain tumours, toxins, brain injury have also been delineated to result dementia (Pekkala, 2004). Other type of AD are sporadic AD and familial AD (FAD). Familial AD generally occur before the age of 60 years and this type AD occur in patients due to the transfiguration in genes detected in three chromosomes (Pekkala, 2004). The transfiguration are derived in an autosomal dominant mode of transmission, they state for less than 10% of AD patients. In most of the patients suffering from AD have dementia syndrome that have usually enhanced later in life and the nature is sporadic.

There are some risk factors that have been recognized or likely to occur sporadic AD, such as lower intelligence, female gender, old age, small scalp volume, melancholy, lower level of

education, older age of woman at time of childs birth, head trauma history, vascular dysfunction of brain, cholesterol, toxins, inflammatory process, hyperthyreosis, down syndrome, and yet to determine the environmental condition that influences it (Pekkala, 2004). The researcher studied that even 20-30 years before the existence of initial symptoms, neuropathology of AD may begin to develop. The collection of phosphorylized tau protein and the generation of beta-amyloid in the extracellular plaques that are likely to ruin neuron in AD (Pekkala, 2004). The other differences include existence of amyloid in the blood vessels, destruction of neurons and neurons and granulovaculonar degeneration. Because of this reason the process of neurotransmission is also affected, it particularly results the damage to the cholinergic transmitter in basal ganglia.

It was observed that in the hippocampus region and the entorhinal cortex located in the medial temporal lobe, there is a great loss of neurons. The connecting links that joins the entorhinal region and the hippocampus with the other cholinergic system in forebrain- part of neural system that is used for learning, behaviour, attention are vulnerable to AD. The brain of AD patients show atrophy of cerebral gyri and associated widening of sulci, dilatation of the lateral and third ventricles and a decrease in weight. The area of brain of AD patients that is most severely involved in the atrophic process are especially entorhinal cortex, hippocampus and the medial temporal lobe.

It has been observed that the abnormal neurological feature are very less visible in the beginning stage of AD, but it seems to appear as the disease advances. The most typical symptoms of AD seem to be slowness of motor movements, extrapyramidal signs (e.g., hypomania, hyperkinesia, rigidity, posture and gait abnormalities), primitive reflexes (e.g., suck and grasp reflexes), as well as involuntary and apractic movements. Behavioural and psychiatric symptoms are present in AD in the form of inappropriate verbal bursts, physical aggression, agitation, irritability, restlessness, and difficulty in sleeping (Pekkala, 2004). Paranoid thoughts, suspiciousness, misidentification of faces, visual and auditory hallucinations, these are common in AD patients (Holthoff et al., 2005).

Apart from that mood swing, eating disorders, disturbed sexual functions, carelessness (Benjamin and Burns, 2007). Another associated symptom with this phase of AD is depression when the declination cognitive function of patient and memory problems are identified as well as the neurochemical changes occur in the neurotransmitter, such as deficiency in serotonin and noradrenalin (Pekkala, 2004). In case of AD there is a large changes occur in cognitive functions that deteriorates slowly and selectively. The increment of deterioration varies person to person (Braak and Braak, 1995).

1.3 Staging in Alzheimers Disease

Simple test for clinical diagnosis of AD have been introduced to check the capability of patients cognitive functions and social behaviour to find out the stage of disease. With these tests results we can the estimate how much part of patients cognitive abilities declined and it can also be estimated that what would be status of disease after couple of years (Suhonen et al.) clinical dementia rating (CDR), Global Deterioration Scale (GDS), and the Mini Mental State Examination (MMSE). The MMSE test can be used to estimate the language function, memory declination and perception, concentration. It is an appropriate and reliable method to estimate the cognitive decrement of the older people (Pekkala, 2004), but it is not that much effective in detecting very mild cognitive decrement in the initial stage of AD. The MMSE score correlates with the age of the patients and the education level. The researcher found that the younger and more educated people tended to perform better comparatively in the test (Pekkala et al., 2006).

1.4 Imaging techniques

Although these tests are necessary to diagnose the Alzheimers disease in early stage but these are not sufficient. To get the accurate result researchers used some imaging techniques; initially CT scan was used then PET, SPET and MRI.

1.4.1 Computer Tomography (CT)

Computer tomography is an imaging technique that produces transverse images, by slicing the tissue from multiple directions using a narrow fan-shaped beam.

1.4.2 Positron mission Topography (PET)

PET is the most recent nuclear imaging technique that measures physiological function like perfusion, metabolism rather than gross anatomy. PET images have higher signal to noise ratio and better spatial resolution than SPECT images.

1.4.3 Single photon emission computer tomography (SPECT)

In single photon emission computer tomography, a rotating gamma camera, with one, two or three detector heads, that rotates around and as closely as possible to the patients. SPECT analysis used to diagnose variety of diseases that cause altered blood perfusion. SPECT scan can be used to measure cardiac wall thickness. Pseudocoloring is applied to obtain more clarity.

1.4.4 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging is a non-invasive imaging technique that uses radiofrequency (0.2GHz-2GHz) higher strength of magnetic fields (around 1-2 tesla), which is almost equals to earths magnetic field of about 0.5×10^{-4}T. MRI images provides the clear vision through which we can extract anatomical and physiological details, that means, construction and activity, with total 3-dimensional view, proper soft tissue envision and large resolution in the spatial domain.

1.5 Objective of the Thesis

The primary objective of this research work is to investigate the pattern associated with the normal and diseased MRI brain image of AD patients. And develop the computerized techniques for the classification of normal and AD images. This techniques includes:

1. Collection of MRI image of AD patients as well as normal MRI brain image of people of different age groups.

2. Developing the patterns in the images using image processing techniques to classify AD images and normal images.

3. Comparison of different techniques used in the entire investigation.

Chapter 2

Literature Review

Chapter 2

LITERATURE REVIEW

2.1 LITERATURE REVIEW

During the past two decades, lot of research have been done in this field regarding the application of image processing techniques for Alzheimer disease diagnosis. Magnetic resonance imaging (MRI) is one of the imaging technique to analyse AD, preferred by doctors for the analysis of patients condition. MRI has produced a beneficial in vivo technique to ingress the deformations that arise in the patients brain during the advancement of AD disease, and provides potential means for recognizing individuals in the preclinical stages. Desikan and Cabral proposed the technique in which they analysed the entire brain. They categorized the MRI data in two classes: whole brain analysis and the voxel of interest (VOI) (Desikan et al., 2009).

Voxel based morphometry (VBM), its an automated entire brain measuring tool, used to analyse the structure of MRI brain image. It facilitates the non-biased measure of highly affected area that may not be accessed in hypothesis based studies. Independent component analysis (ICA) techniques was also used for signal separation. This data driven method involves two or more variable quantities that quantifies the analytic examination of magnetic resonance imaging datasets which produces some unique patterns about the similarity between the smallest units of three dimensional image called voxels in the specific portion of the human brain. Some of the machine learning techniques has been used for detection and classification of patients with AD and mild cognitive impairment (MCI), such as ANN, SVM, LS-SVM etc.
.

A novel method was also proposed that used ICA to obtain the unique patterns from VOI and execute machine learning techniques mentioned above, for separating the AD controls from the healthy controls and achieved 87.3Huang and Prinz analysed the various spectral and nonlinear EEG that is used to detect the brains functional changes in the Alzheimers disease.

They extracted the specific features from EEG that demonstrate the staging of the disease. They used sixteen AD patients with AD, their ages were between 61-82. The extracted features from the EEG includes: Power spectral measurements, chaotic features, ERP features, after determining the features they used artificial neural network technique to classify the results (Huang et al., 2000).

Zhang integrated the multimodal imaging and non-imaging via a weighted combination of multiple kernels, which provides the improvements in the problems of discriminating Alzheimer disease (or mild cognitive impairment (MCI)) and healthy controlled subjects (Zhang et al., 2007).

Freeborough and Torabi used the same technique in an uncommon way. They also used the MRI brain images 51 healthy brain images and 42 abnormal ones, split in to two groups : training data and the testing data. They used 65% of each group for training process and rest of the groups were used for testing purposes and develop an effective algorithm to analyse MRI data sets in order to recognize Alzheimers disease. The feature of interest are categorized in features of frequency domain (FFD) which are based on the first four static moments of the wavelet transform. Extracted features were classified by a multi-layered perceptron Artificial Neural Network (Torabi et al., 2006). Before ANN, the number of features is reduced from 44 to 12 to optimize and eliminate any correlation between them using principal component analysis (PCA). PCA is used to reduce the number of features to decrease the time needed in processing. 12 FFDs and 32 FSDs is used. FFD is obtained by applying wavelet transform on the image gray-level matrix and FSD is obtained by computing GLCM. And for static moment following parameters were calculated: mean of the wavelet coefficients, stander deviation of the wavelet coefficients, skewness of wavelet coefficients (skewness is the measure of asymmetry of data around the sample mean), Kurtosis of the wavelet coefficients (Kurtosis is a measure of how outlier-prone a distribution is. Also it can be considered as the measure of the sharpness of the histogram). They got 21% error with test set and no error with the training set and 100% accuracy among the training data.

In recent studies, some phenomena in the brain have become popular for AD diagnosis, e.g., some type of brain atrophy, the number of senile plaques, size of senile plaques in patients brain, deformation occur in shape of the brain, brain shrinkage and the pattern of neuroanatomic which will change if AD appears.

Ceyhun and Devrim proposed two approaches to determine the similarity between the different cases. While the first approach by implication utilizes the separation to support vector machine decision boundary as a similarity index measurement. And the other one targets at directly finding the similarity function based on the minimization of the empirical ranking risk. They used neural network approach to detect Alzheimer disease in early stages using visual

similarity and user feedback system. Depending on the similarity based score, they classified the disease (Akgl et al., 2009). The proposed similarity learning based NN results highly precise AD prediction even with the global descriptor that indicate the presence of Alzheimer disease after the certain interval of time. Gleckman propounded a method in which we use segmentation technique for different types of brain tissue: gray- matter (GM), white matter (WM) against cerebrospinal fluid (CSF) in the MRI to find the brain atropy. Atrophy based estimation finds the reduction occur in the whole brain. To calculate the atropy (AT) only gray matter, white matter, is considered in comparison of cerebrospinal fluid in an MRI image. With the help of AT we are also able to indicate other diseases like Picks disease, multiple sclerosis. Alzheimer disease factor (Gleckman, 2007), and differentially diagnosed Alzheimer disease factor (DDAD) are also propounded to indicate the atrophy associated with early AD stages for the detection in first MRI and multiple subsequent MRIs respectively (Sadek, 2012).

These approaches offer easy reliable detection of the brain atrophy for the brain attacked by a neurodegenerative disease even before cognitive symptoms interfere with daily function. Schaefer and his team presented a pattern recognition method, by utilizing the typical statistical features, histogram features, mutual information based features and cross co-occurence matrix features as the feature extraction method and applied those features to classifier based on Fuzzy rule to classify the images (Fernndez et al., 2009). The classification rate of this classifier is 79% with the help of 14 partitions fuzzy.

Chapter 3

Materials and Methods

Chapter 3

MATERIALS AND METHODS

3.1 Introduction

Pattern recognition is primarily related to the depiction and the order of estimations taken from the physical and mental procedures. Numerous definitions have been proposed in order to process the information and to produce an effectual and a well-organized depiction of patterns, pre-processing is generally we do to detach the noise from the information signal. Then the group of typical measurements, which may be non-numerical or numerical, and the connections between the measurements taken from the special pattern are extricated for the rendition of the pattern. The depiction or classification of the patterns is performed in order to achieve the special goal.

In order to get an effective set of characteristic estimations and their relations for the depiction of patterns, we always focus on the goal, for that a prudent investigation is required. The main objective of the pattern recognition is to estimate the correct level corresponding to given set of features based on the experience obtained through the training process. The pattern recognition can well understood by taking an example: when we go to school for the first time teacher uses the picture of apple to teach us. We observe the shape, colour, structure, and the word that is associated with that shape. On the basis of their shape and colour we recognize the object. Then we start learning alphabets in the same way we observe the straight lines/curves made by the teachers for the particular alphabet. Here straight lines/curves are the set of features to recognize the specific alphabet. And we keep practicing continuously to achieve the correct level of accuracy.

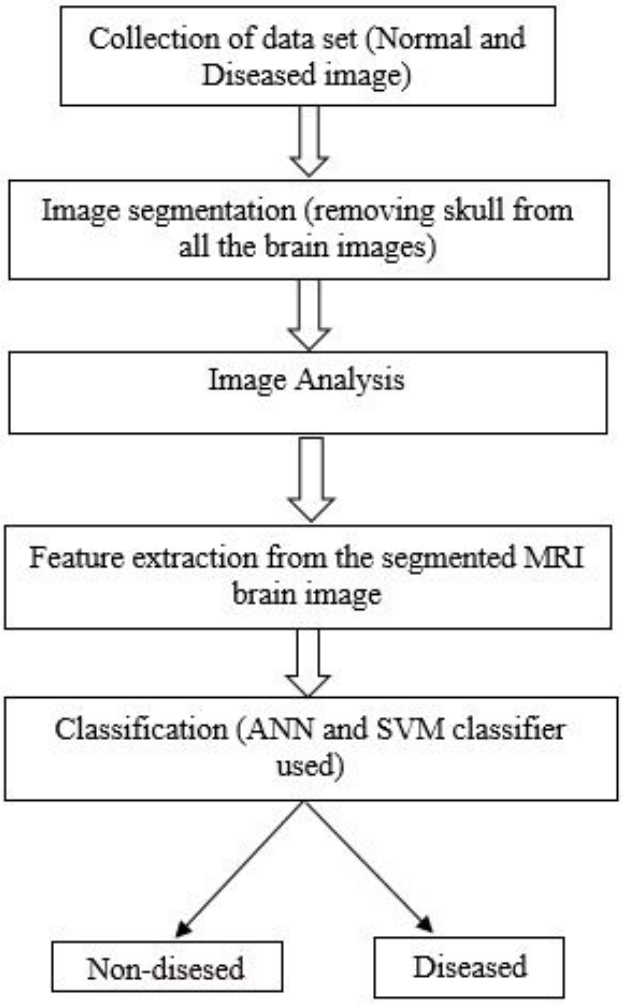


Figure 3.1: Flow Chart of Used Methodology.

Scientifically it was proven that even the new born baby is able to recognize his/her mother, they know the specific smell produced by his/her mother. In case of a new born baby, that unique smell works as a key feature for the baby. In the same way our pattern recognition system works.

The main objective of my project work is to classify the normal and Alzheimers disease MRI brain images, using pattern recognition and different image processing techniques. The pattern recognition system for the classification task is given by the Flow chat as shown in the Fig. 1.

3.1.1 Overview of Data Set

The Open Access Series of Imaging Studies (OASIS) consist of large collection of MRI brain scan. This huge collection of data set is composed of all the MRI scan belongs to neural disease including Alzheimers disease for study purposes.

Table 3.1: Details of healthy subjects.

ID	SEX	HAND	AGE	MMSE	CDR
OAS1_0206_MR1	F	R	78	30	0
OAS1_0207_MR1	M	R	51	29	0
OAS1_0208_MR1	F	R	55	28	0
OAS1_0212_MR1	F	R	74	30	0
OAS1_0216_MR1	F	R	71	30	0
OAS1_0220_MR1	F	R	75	29	0
OAS1_0221_MR1	F	R	94	28	0
OAS1_0228_MR1	F	R	81	30	0
OAS1_0229_MR1	F	R	55	30	0
OAS1_0262_MR1	F	R	73	29	0
OAS1_0264_MR1	F	R	77	25	0
OAS1_0265_MR1	M	R	90	30	0
OAS1_0268_MR1	F	R	67	30	0
OAS1_0269_MR1	M	R	33	30	0
OAS1_0270_MR1	F	R	63	30	0
OAS1_0271_MR1	F	R	49	30	0
OAS1_0272_MR1	F	R	60	30	0
OAS1_0274_MR1	M	R	43	30	0

The data set consist of 416 subjects aged 18 to 96 years, including 218 subjects aged 18 to 59 years and 198 subjects aged 60 to 96 years. Of the older subjects, 98 had the clinical dementia rating (CDR) score of 0, indicating no dementia, 100 had a CDR score greater than zero (70 CDR=0.5, 28 CDR=1, 2 CDR=2), indicating a diagnosis of mild of very mild to moderate AD. The detailed statistics of the data was described in the literature (Marcus et al., 2010). In this project work, we mainly focus on the patients suffering from Alzheimer disease from the age matched healthy subjects. Therefore we have taken all brain scans which falls in the category with CDR value 0.5, 1 and 2 as the AD control subjects.

3.2 Image processing

Mechanism of transforming an image into an advance digital domain and execute some operation on it, in order to obtain the aggrandized image or to extricate the valuable data from it, is known as image processing. Image processing encompasses processes whose inputs and outputs are images and, in addition, encompasses processes that extract attributes from images,

Table 3.2: Details of AD subjects with CDR=0.5.

ID	SEX	HAND	AGE	MMSE	CDR
OAS1_0205_MR1	M	R	75	30	0.5
OAS1_0210_MR1	F	R	73	28	0.5
OAS1_0217_MR1	F	R	78	27	0.5
OAS1_0226_MR1	M	R	90	23	0.5
OAS1_0022_MR1	F	R	69	23	0.5
OAS1_0023_MR1	M	R	82	27	0.5
OAS1_0039_MR1	M	R	70	29	0.5
OAS1_0041_MR1	F	R	62	28	0.5
OAS1_0042_MR1	M	R	80	29	0.5
OAS1_0046_MR1	M	R	64	22	0.5
OAS1_0060_MR1	M	R	79	29	0.5
OAS1_0066_MR1	F	R	66	28	0.5
OAS1_0390_MR1	M	R	69	24	0.5
OAS1_0400_MR1	F	R	92	25	0.5
OAS1_0402_MR1	F	R	76	30	0.5
OAS1_0411_MR1	F	R	71	29	0.5
OAS1_0418_MR1	M	R	74	28	0.5

and including the recognition of individual objects. In this project work, I utilized two methods of image processing.

(a) Image segmentation

(b) Feature extraction

3.2.1 Image Segmentation

The task of partitioning the image into coterminous components which represents the unique and meaningful information for further analysis of data is known as the segmentation. In other words, segmentation subdivides the image into its constituent regions or objects. The level of detail to which the subdivision is carried depends on the requirement. That is, segmentation should stop when the object or the region of interest in an application have been detected. Some segmentation technique that is fully automated have their own advantages and disadvantages.

To perform the segmentation process the MRI image should be spotted with the region of interest, and to make the segmentation operation uncomplicated detach the skull present in MRI image of brain to obtain better results.

Table 3.3: Details of subjects with CDR=1.

ID	SEX	HAND	AGE	MMSE	CDR
OAS1_0028_MR1	F	R	86	27	1
OAS1_0031_MR1	M	R	88	26	1
OAS1_0035_MR1	F	R	84	28	1
OAS1_0052_MR1	F	R	78	23	1
OAS1_0053_MR1	F	R	83	21	1
OAS1_0056_MR1	F	R	72	15	1
OAS1_0067_MR1	F	R	71	27	1
OAS1_0073_MR1	F	R	69	21	1
OAS1_0388_MR1	F	R	77	22	1
OAS1_0399_MR1	M	R	78	29	1
OAS1_0405_MR1	M	R	75	23	1
OAS1_0308_MR1	F	R	79	15	2

3.2.2 Skull Stripping

STEP -1 Grayscale to binary conversion Convert the grayscale MRI brain image into binary image. In the binary image all the pixel value greater than the level of luminance are replaced by 1 and the pixel value smaller than the level of luminance are replaced as 0.

STEP-2 Filling the interior gaps We made all the pixel value inside the skull boundary, greater than the level of luminance. That is, all the pixel value inside skull boundary is replaced by 1. We have filled the holes of binary image present inside the skull boundary to obtain the cleaned binary image.

STEP-3 Erosion of cleaned binary image Erosion operation is performed on the image. Gray-level erosion reduces the brightness of the pixels that are surrounded by the neighbours with a lower intensity.

insert formulae

In Erosion operation we assign all the pixel value as 0, present at the outer boundary of the image. Which results the image in which outer objects are removed. Which results the eroded binary image.

STEP-4 Remove the connected objects on the border We used the eroded binary image as a mask. We multiply the eroded binary mask with the original image. It multiplies the all the pixel value of the original image with all the corresponding pixel value of eroded binary mask. Which results the desired MRI image without skull.

3.2.3 Analysis of Data Set

We categorized all the subjects into three groups according to their CDR value. We considered the healthy subjects with zero CDR score in first category. Second category consist of mild dementia patients having CDR score half. And the third category consist of severe case of AD with CDR value one. All the subjects belong to the age from 40 years to 80 years. We

Table 3.4: Details of subjects, here MMSE-Mini Mental State Examination and CDR-Clinical Dementia Rating.

ID	SEX	HAND	AGE	MMSE	CDR	Brain area lost in middle section (pixels)
OAS1_0293_MR1	F	R	69	26	0	848
OAS1_0216_MR1	F	R	71	30	0	1521
OAS1_0237_MR1	F	R	72	27	0	1771
OAS1_0280_MR1	F	R	78	30	0	1938
OAS1_0075_MR1	F	R	83	30	0	2034
OAS1_0201_MR1	F	R	85	26	0	2181
OAS1_0022_MR1	F	R	69	23	0.5	1474
OAS1_0411_MR1	F	R	71	29	0.5	2313
OAS1_0298_MR1	F	R	72	24	0.5	2047
OAS1_0287_MR1	F	R	78	21	0.5	1919
OAS1_0380_MR1	F	R	83	18	0.5	2617
OAS1_0304_MR1	M	R	85	29	0.5	4109
OAS1_0073_MR1	F	R	69	21	1	2849
OAS1_0067_MR1	F	R	71	27	1	2321
OAS1_0056_MR1	F	R	72	15	1	2340
OAS1_0052_MR1	F	R	78	23	1	2285
OAS1_0053_MR1	F	R	83	21	1	2460
OAS1_0035_MR1	F	R	85	28	1	3224

calculated the area of the middle part of the brain that includes Septum Pellucidum, Fornix and some part of Thalamus, this is our area of interest here. Then we analysed the percent change occur in area of interest of different age group subjects. We saw that gray matter and white matter present in that area decreases as the age increase from 40 years to 80 years. We have done the same analysis for all groups.

In further analysis we calculated the total area which also includes area associated with the central section. We calculated the area of all the MRI images present in data set separately. And the value of area is in pixels that means we simply used the tool present in MATLAB bwarea which calculates the area of objects in binary image. The total area is the scalar quantity value corresponds to the total number of on pixels in the image, but might not be exactly the same different patterns of pixels weighted differently. In this analysis our aim is to calculate the percentage area of total visible gray matter/ white matter along with brain parts present in MRI brain image. To calculate the total visible area of MRI brain image following steps are involved

STEP-1 Calculate the area of brain part lost in centre section as we did in previous analysis.

STEP-2 Calculate the area entire brain along with the area of central section that we have already calculated.

STEP 3 Apply the formulae shown below that gives the percentage area of gray matter/white

Table 3.5: Percent of gray/white matter present in different age group subjects.

No. of subjects of same age	Age	%G with CDR=0	%G with CDR=0.5	%G with CDR=1
3	69	95.47	91.86	84.22
3	71	91.48	87.79	87.67
3	72	90	88.05	87.04
3	78	89.59	89.45	87.71
3	83	88.8	85.61	85.23
3	85	87.76	76.72	81.78

matter present in the MRI brain image as shown in Table 3.5.

$$G = [(A_{total} - A_{ROI}) \times 100] \div A_{total} \tag{3.1}$$

Where G= percent of gray matter/white matter present in the MRI brain image

AROI = Area of the central section

3.3 Segmentation to detect Hippocampus Area

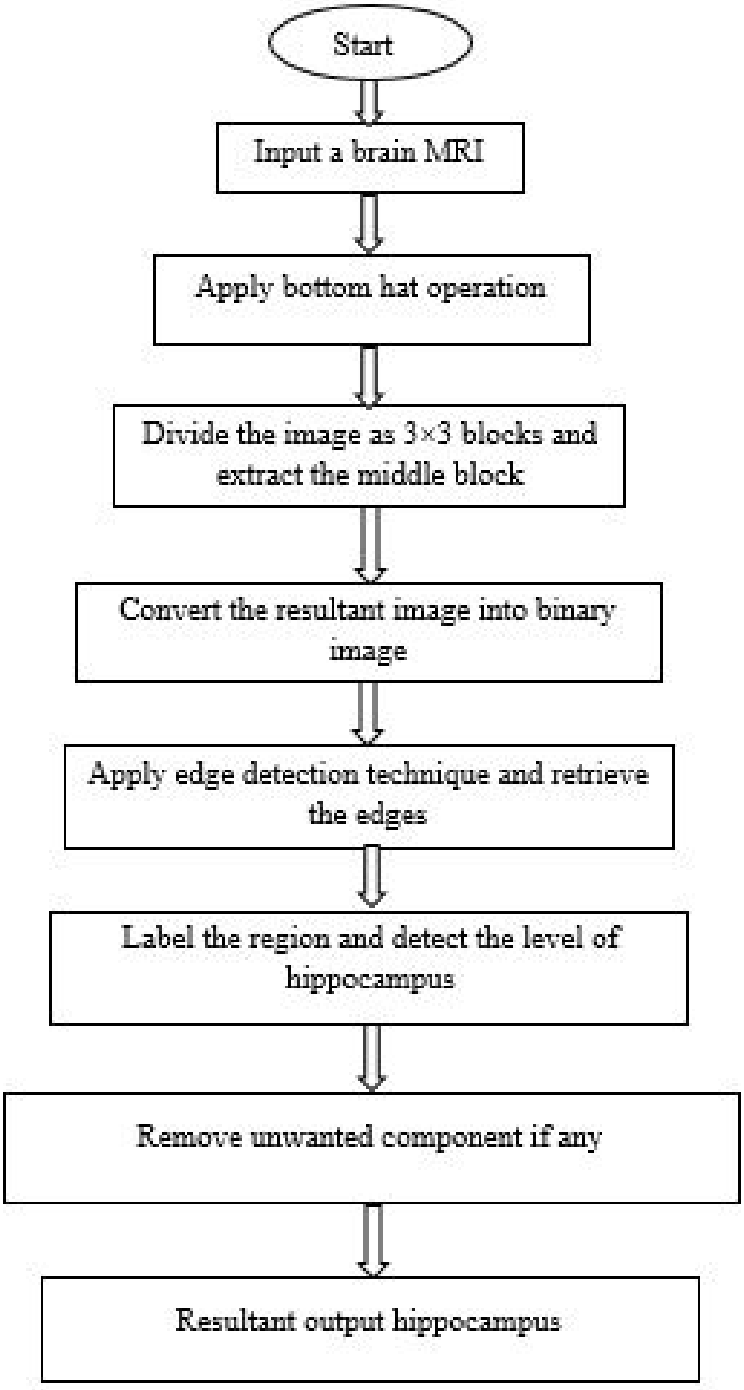


Figure 3.2: Flow chart to Detect Hippocampus area of MRI Image.

3.3.1 Bottom hat operation

Bottom-hat morphological operator subtracts input image from the result of morphological closing on the input image. We apply the Bottom-hat operation on the binary image, the filter permits getting all object parts, which were added by closing filter, but we were not eliminated after that because of the formed connections and joints.

3.3.2 Partition of image into 33 blocks

To split the image into 33 blocks, the total number of rows associated with the MRI brain image are divided by 3, which generates row wise three blocks of image. In the same way when total number columns of the resultant matrix associated with resultant image are also divided by 3. It generates the total 9 matrices or 9 blocks of image.

3.3.3 Binary conversion and edge detection

To split the image into 33 blocks, the total number of rows associated with the MRI brain image are divided by 3, which generates row wise three blocks of image. In the same way when total number columns of the resultant matrix associated with resultant image are also divided by 3. It generates the total 9 matrices or 9 blocks of image.

3.3.4 Binary conversion and edge detection

To convert the gray scale image into binary image we used I=im2bw( ), this syntax replaces all the pixel value present in the MRI brain image with luminance greater than the specified level with the value 1 (white) and the rest of the pixels replaced with 0 (Black). We set the level in the range of 0 to 1. To get the better binary image we tried the level 0.2, 0.3 and 0.4. We got the best result with 0.3 for most the MRI brain images. In edge detection operation, we basically catch the area in the MRI brain image where the sudden change in intensity level take place. For the edge detection we have used two types of detectors canny edge detector and sobel edge detector. Canny uses two different value of threshold, one for strong edge and other for weak edge, but weak edges will be there in output only if it is connected with the strong edges. If the weak edges are not connected with the strong edges it will not appear in the output image.

3.3.5 Labelling of Region

This operation lebels the input binary image, the background is having the pixel value 0 (Black) and the foreground image is represented by the pixel value 1. If the there is more than one object is their in the image then the second object is represented by the label 2.

3.4 Feature Extraction

Feature extraction is a technique in which we perform some operation and different filtering techniques, as per our requirements, on the image and extract the meaningful and unique information and also used for the dimensionality reduction. We used three different feature extraction methods (Haralick et al., 1973), chip histogram based texture feature, wavelet based texture features and trauma texture features to extract the various features from the segmented MRI image of brain.

3.4.1 Chip histogram based texture feature

For the grayscale image let the number of gray level be L, so there exist the gray vectors, which varies from 1 to L. The histogram of the grayscale image is given as Histogram= h(rk)=nk, where rk is the kth gray level, nk is the number of pixels in the image having gray level rk and h(rk) is the histogram of a digital image with gray level rk (Wei et al., 2014). The image having size of MN, Gray level probability function is defined as:

$$Graylevelprobablity = P_{(rk)} = \frac{h_{(rk)}}{M \times N} \tag{3.2}$$

The chip histogram features are extracted from each normal and AD images. These features are:

(a) Mean: It is defined as the average of all the pixel values present in an image.
It is given by:

$$Mean(\mu) = \sum_{r_k}^{L} P(r_k) \times r_k \tag{3.3}$$

(b) Varience: It is defined as the expected value of square of the standered deviation of gray level of an image from its mean.
It is given by:

$$Varience(\sigma^2) = \sum_{r_k=1}^{L} P(r_k) \times (r_k - \mu) \tag{3.4}$$

(c)Kurtosis: It is a measure of sharpness of the peak of the probability distribution func-

tion corresponding to that image. The image with high kurtosis value tend to have different peak near the mean value and decline rapidly. Similarly the image having low value of kurtosis tend to have flat top near the mean rather than sharp peak.
The Kurtosis of distribution can be formulated as:

$$Kurtosis(Ku) = \frac{\sum_{r_k}^{L} P(r_k) \times (r_k - \mu)^4}{\sigma^4} \tag{3.5}$$

(d)Skewness: It is the measure of asymmetry of the probability distribution function about the mean corresponding to the image. If the skewness is negative, then the pixels in the image are spread out more to the left of the mean than to the right. Similarly, if the skewness is positive, the pixels in the image are spread out more to the right of the mean than to the left.
Skewnes can be given as:

$$Skewness(S) = \frac{\sum_{r_k}^{L} P(r_k) \times (r_k - \mu)^3}{\sigma^3} \tag{3.6}$$

(e)Entropy: The statistical measure of randomness that can be used to charactorize the texture of image known as entropy of that image.
Entropy is given by:

$$Entropy = -\sum_{r_k=1}^{L} P(r_k) \times \log(P(r_k)) \tag{3.7}$$

(f) Energy: Energy gives the concepts about the measure of information. It can be calculated by using the probability distribution function.

$$Energy = \sum_{r_k}^{L} P(r_k)^2 \tag{3.8}$$

3.4.2 Wavelet based texture feature

Wavelet tool is used to decompose an image. Apart from that it is also used for image compression. Decomposition of image take place by passing the image through a series of low-pass and high-pass filter and if we reverse the process of decomposition, we are able to get the same image (Kingsbury, 2001). After decomposition new low-pass and high pass regions are formed. The level of decomposition depends on the number of repetition of process, along with that it gives average intensity properties as well as contrast level distributed throughout the image.

Wavelet provides better texture classification (Unser and Aldroubi, 1996). Wavelet transform also used in the field of telecommunication and biology. Since we can easily analyse the non-stationary signal, it became a powerful alternative tool for Fourier method in many medical applications. The key point about the wavelet is that they have variety of window length that we can use, wide window for less frequency signals and narrow window for the high frequency signal. In case of image, their rows and columns are operated separately in each direction which results a pass image LL and three other images like HL, LH and HH. The low horizontal and high vertical frequencies information contained in the LH channel, high horizontal and low vertical frequency information contained in the HL channel, and the high horizontal and high vertical frequency information contained in HH channel. The wavelet coefficients of images are:

$$W_{\phi}(j_0,m,n) = \frac{1}{\sqrt{M \times N}} \sum_{x=0}^{M-1} \sum_{y=0}^{N-1} f(x,y) \phi_{j_0,m,n}(x,y) \tag{3.9}$$

$$W_{\psi}(j_0,m,n) = \frac{1}{\sqrt{M \times N}} \sum_{x=0}^{M-1} \sum_{y=0}^{N-1} f(x,y) \psi^{i}{}_{j_0,m,n}(x,y), i = \{H,V,D\} \tag{3.10}$$

where

$$\psi^{i}{}_{j,m,n}(x,y) = 2^{j/2}\psi(2^{j}x-m,2^{j}y-n), i\{H,V,D\} and \phi_{j_{0,m,n}}(x,y) = 2^{j/2}\varphi(2^{j}x-m,2^{j}y-n) \tag{3.11}$$

are scaled and translated basis functions

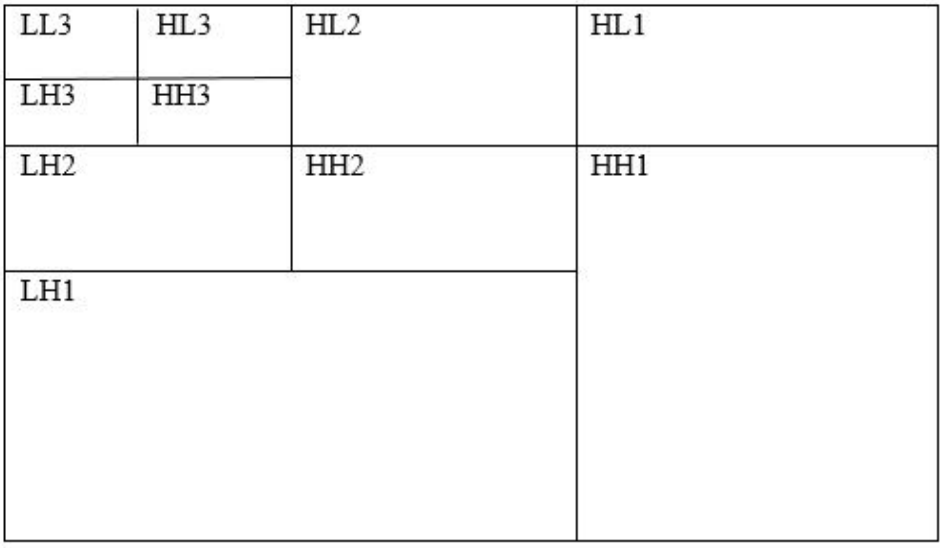


Figure 3.3: Horizontal,vertical and diagoanl details of three level wavelet based image decomposition.

Chapter 4

Machine Learning

Chapter 4

MACHINE LEARNING

4.1 Introduction

Machine learning mainly concern with the design of algorithms which makes the computer to learn. Machine learns everything from the given data set and associated features with a data. There are different leaning methods for the statistical data analysis. These are supervised and unsupervised learning.

Supervised Learning is the machine learning task that is widely used to generalize the input output relationship and generate the predicted output for an unseen input. The goal of supervised learning is to classify the objects. In the supervised learning some data or objects are analysed to get some unique information which makes the object different from other such as length, Width, color, area etc, that means with the help of this predetermined features about the objects we prepare a training feature set which helps to train the computer. When we feed a new object in the computer for testing purpose computer extract all the feature of new object and compare it with the predetermined feature set that is already stored in the computer and classify the object. The accuracy of the classification is totally depend on the training feature set. If the training set is not sufficient then it will not classify object correctly. So during feature extraction it is necessary to obtain all the information associated with the training object.

The goal of Unsupervised Learning is not related to the future observation. In this learning computer have to learn classify the objects on its own without having any information about the objects unlike supervised learning.

4.1.1 Classifiers

We have used two classifier ANN (Artificial Neural Network) and SVM (support vector machine) to classify the new test data set. These classifiers come under supervised learning task.

In machine learning the classification is basically the task of identifying, to which class the new observation belongs. The computer program which is used for the classification is known as classifier.

4.1.2 Artificial Neural Network

Artificial Neural Networks (Greenberg, 2004) is a type of artificial intelligence that imitates some functions of the persons mind. ANN has a normal tendency for storing experiential knowledge. An ANN consists of a sequence of layers, each layer consists of a set of neurones. All neurones of every layer are linked by weighted connections to all neurones on the preceding and succeeding layers (Matas et al., 2008). Artificial neural networks are data driven self-adaptive technique that is designed in such a way that it mimics the neural function of the human brain to a great extent. ANN are consist of large number of simple processors with a number of interconnections associated with it which works simultaneously to solve a specific task in machine learning. It uses non-parametric approach. Its performance and accuracy depends upon the network structure and number of inputs. In this project work we used Multilayer feed forward neural network (MFNN) as a classifier to classify the Alzheimer patients from the normal subjects.

4.1.3 Multilayer feed forward Neural Network (MFNN) Classifier

MFNN consist of three layers: input layers comes first which consist of input variables. Then output layer which is the last layer of this design. Hidden layer comes between these input and output layers.

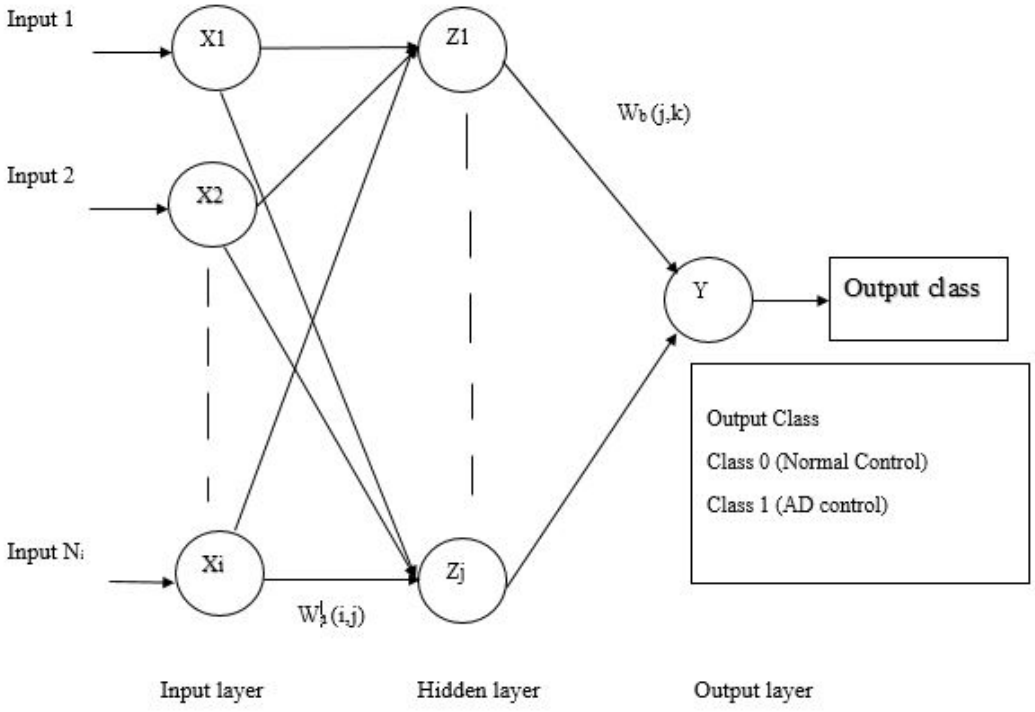


Figure 4.1: Block diagram of Multilayer feed forward Neural Network.

4.1.4 Support vector machine (SVM)

SVM and LS-SVM (Least Square Support Vector Machine) is also based on the supervised learning. These classifiers are also used to solve the problem of classification in machine learning. The features that is extracted from the previous stage, acts as the input to these classifiers and it is directly given to these classifiers. Classifiers estimates, to which category the input features belong to. A support vector machine builds a hyper plane or set of hyper planes in a high or infinite dimension space, used for classification. Good separation may be achieved by the hyper plane that has the largest distance to the nearest training data point of any class (functional margin), larger the margin lower the generalization error of the classifier (Cristianini and Shawe-Taylor, 2000). SVM uses non parametric with binary classifier image and can handle more input data very efficiently. The performance and accuracy depend upon the hyper-plane section and kernel parameter.

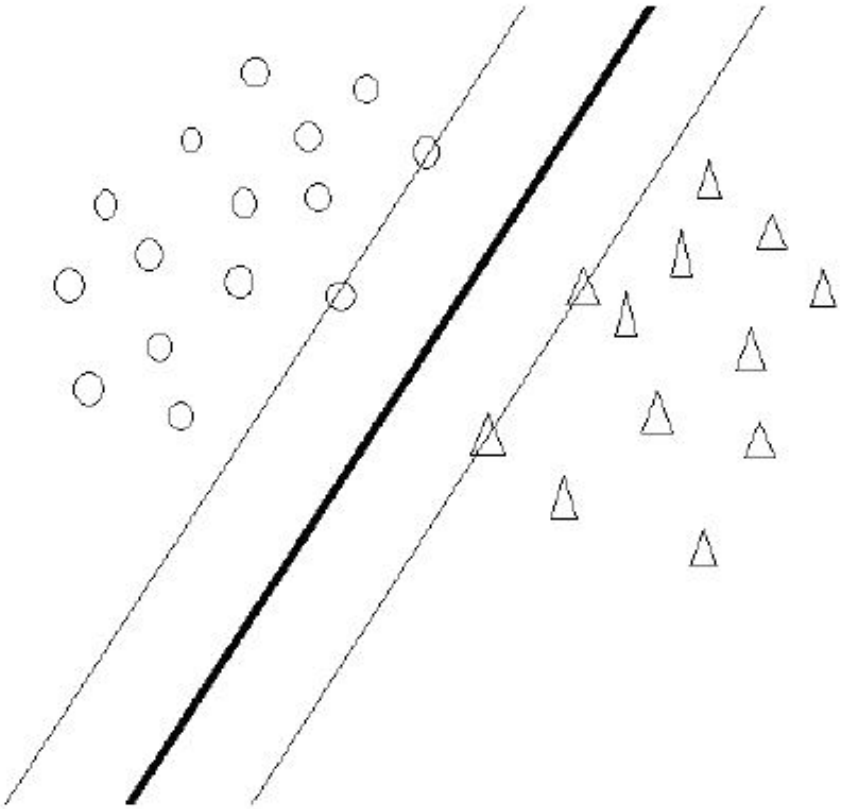


Figure 4.2: Working of SVM for the nonlinear separable data (triangle symbol used for diseased and circle for non-diseased category).

4.1.5 Criteria for the performance of classifier

Factors such as CR (classification rate), Sensitivity, Specificity, and Receiver operating characterstic (ROC) decides the performance of the classifiers (Lu et al. 2004). the values can be calculated by confusion matrix as shown below:

TP	FN
FP	TN

Figure 4.3: TP: Number of True Positives, FP: Number of False positives, TN: Number of True negatives, FN: Number of False negatives.

$$CR = \frac{(TP+TN)}{TP+TN+FP+FN} \tag{4.1}$$

Sensitivity-It measures of how well a binary classifier correctly identifies the positive cases.

$$Sensitivity = \frac{(TP)}{TP+FN} \tag{4.2}$$

Specificity- It measures of how well a binary classifier correctly identifies the negative class.
ROC Curve-It gives the relation between hit rate and false rate in a noisy communication channel.The performance of the classifier can be determined by considering the area under the curve.

Chapter 5

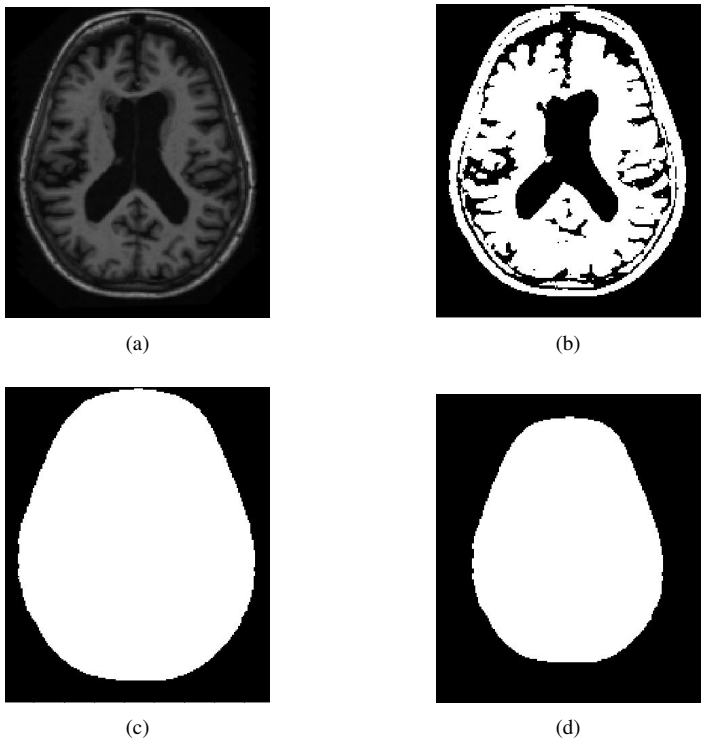
Result & Discussion

Chapter 5

RESULT & DISCUSSION

5.1 Segmentation results

In the beginning, segmentation technique is utilized to remove the skull part present in the MRI images of data set.



(a) (b)

(c) (d)

Figure 5.1: Shows (a) Original image, (b) Binary image, (c) Cleaned image, (d) Eroded image.

The outcomes obtained by performing operations, that we have used in the segmentation

processIn the beginning, segmentation technique is utilized to remove the skull part present in the MRI images of data set. The outcomes obtained by performing operations, that we have used in the segmentation process.

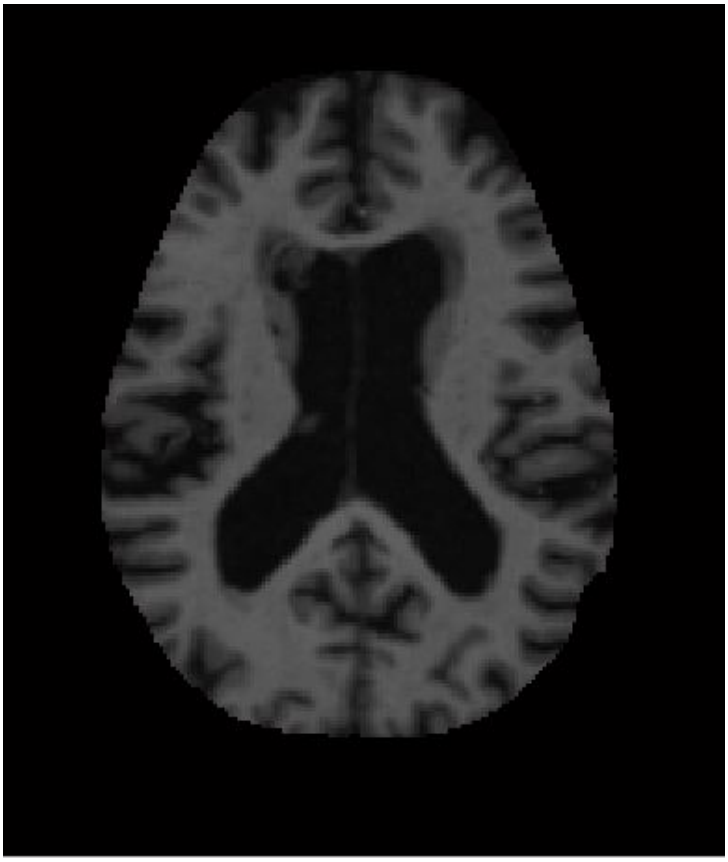


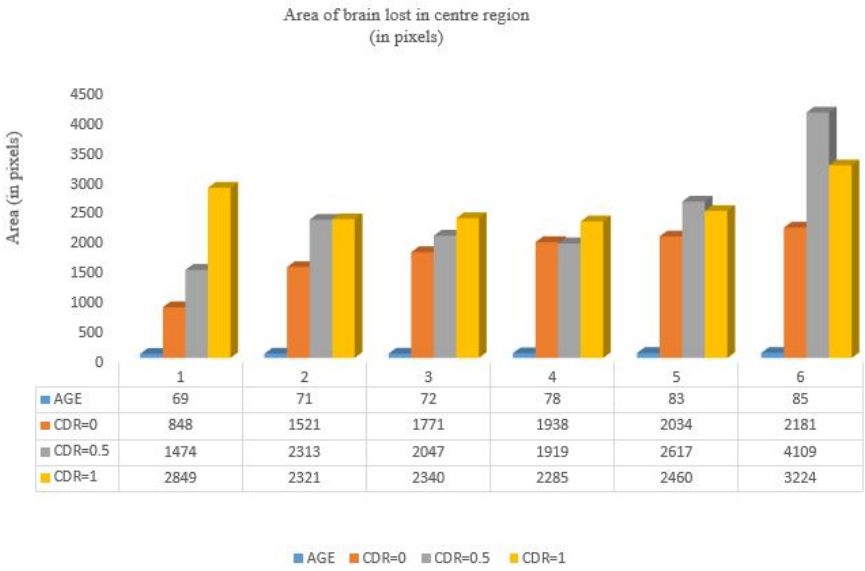
Figure 5.2: Original image without skull.

After segmentation, we analysed some parts of brain which changes as grow older and in case of Alzheimer disease. Most affected area of brain part is its middle part which involves hippocampus, Septum Pellucidum, Fornix and some part of Thalamus. We calculated the area of brain part lost in the central region. It gives an approximate idea about the subjects conditions. We categorised the subjects into three groups according to their CDR value, to analyse the brain loss occur during aging and in case of AD as we discussed earlier. First group of subjects (healthy subjects) have CDR value zero. Second group have CDR value half. And the last group is the severe case of AD, have CDR value of one. Details of the subjects is given in Fig. 3.5.

In the figure shown below blue colour indicates the age of subjects, orange colour bar shows the area of brain part lost in middle section of MRI image with CDR rating 0. Similarly grey

colour indicates the area of brain part lost in middle section of MRI image with CDR rating 0.5. And the yellow colour indicates the brain part lost in the middle section of MRI image with CDR rating 1.

As shown in figure as the age increases brain loss in middle section increases in case of normal control subjects. In second case with CDR is equal to 0.5, it also follow the same brain loss pattern approximately, But the variations come in last case with CDR=1, as shown in figure although the first subject was younger among rest of the subjects, still he suffered from severe brain loss as compared to other subjects. the only reason behind this unusual variation is that the brain loss also depends on several other factors, which includes the environment in which the subject is living, the education level, habit of drinking alcohols, and his daily life work, and how their relatives taking care of the patients.

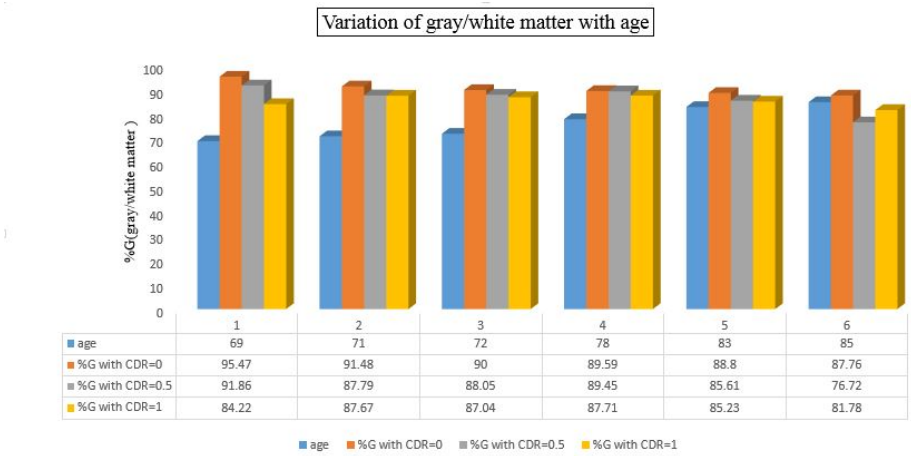


	1	2	3	4	5	6
AGE	69	71	72	78	83	85
CDR=0	848	1521	1771	1938	2034	2181
CDR=0.5	1474	2313	2047	1919	2617	4109
CDR=1	2849	2321	2340	2285	2460	3224

Figure 5.3: Area lost in mid section.

In this analysis we observed that sometimes brain loss is larger in case of patients belong to 0.5 CDR category as compared to the CDR category of 1. Due to this single variation we cannot present any specific pattern of brain loss in MRI image. But this problem is removed in further analysis. We calculated the percentage of gray/white matter present in MRI brain image. When we plot the graph, the saw that the there is continuous decline in brain loss when we compared the subjects of same age of different category. The result also indicate that the as the age increases the rate of brain loss increases rapidly. How much percentage of brain parts along with gray/white matter present in the MRI image, is shown in the table given below.These differences lead us to categorise the normal and AD control subjects. %G as in Table 3.5 which

indicates the percent of gray/white matter present in the MRI image. The subjects belong to the category with CDR=0, are normal healthy persons. They do not suffer from that much brain loss as indicated in the table. On the other hand in case of other two categories with CDR=0.5 and 1, these subjects suffered from severe brain loss. The table indicates that the 10-25% brain loss occurred in these subjects. And in case of subjects belong to first category maximum 12% of brain loss occurred.



	1	2	3	4	5	6
age	69	71	72	78	83	85
%G with CDR=0	95.47	91.48	90	89.59	88.8	87.76
%G with CDR=0.5	91.86	87.79	88.05	89.45	85.61	76.72
%G with CDR=1	84.22	87.67	87.04	87.71	85.23	81.78

Figure 5.4: Variation of white/gray matter with age.

5.1.1 Results of Regional analysis of MRI Brain Image

We analysed the both diseased and non-diseased MRI brain images. In this analysis, initially we considered only the central section which include Septum Pellucidum, fronix and hippocampus area.

5.1.2 Analysis of inner Brain of MRI Image

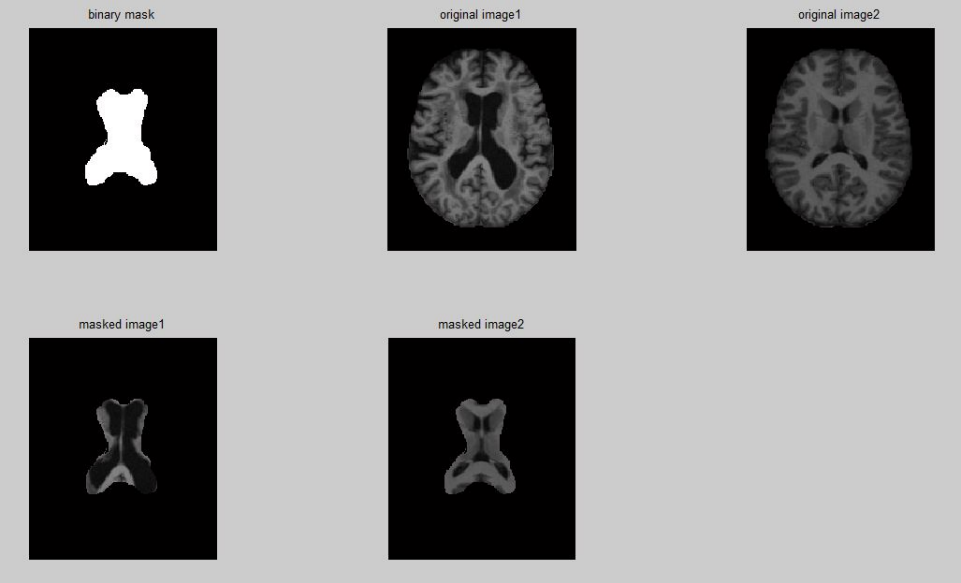


Figure 5.5: Masked image1 and masked image 2 shows only central region of MRI brain image.

In the above figure original image 1 is the diseased one and original image 2 is non diseased MRI brain image. We masked the outer section of both the images to extract the hippocampus volume. These two masked images shows that how much percentage of black region present in the central section of brain image. This part can also be presented in a more better way through histograms as shown in Fig.5.7. when we analysed the histogram of normal MRI brain image, we found that the density of intensity level is greater in between 80 to 100. Whereas in case of diseased MRI brain image, when we analysed the histogram of central section, we got the higher density of intensity level in between 0 to 20. That indicates that in the diseased MRI brain image most of the area is covered by black pixels. This analysis gives a rough idea to classify the images on the basis of volume covered by black pixels by plotting the histogram of the MRI brain image.

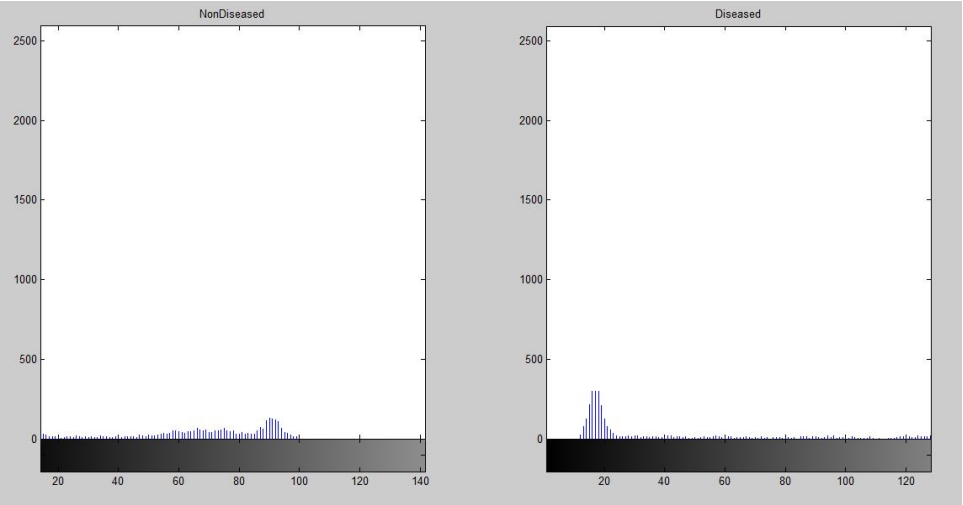


Figure 5.6: Histograms of masked image 1(Right) and masked image 2 (Left).

5.1.3 Analysis of outer brain of MRI image

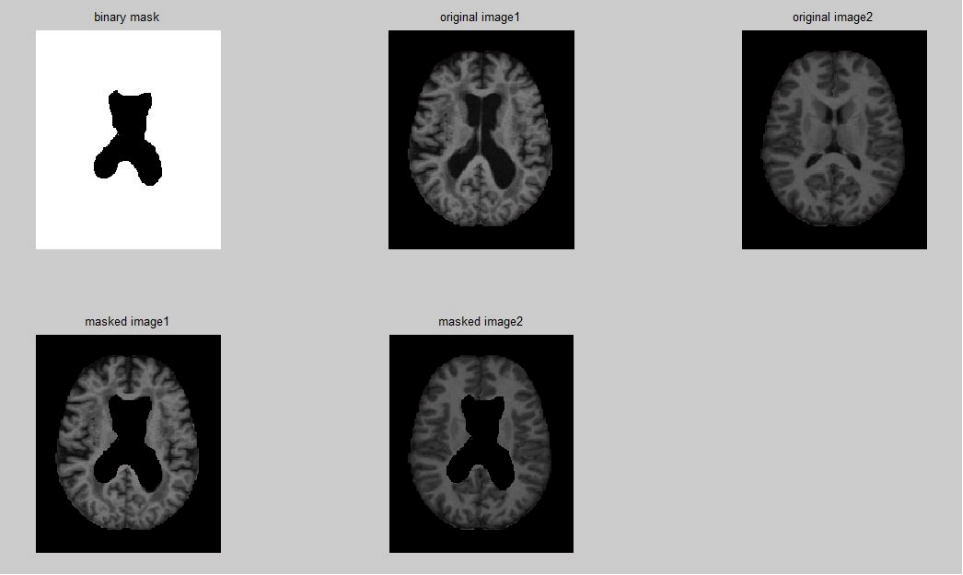


Figure 5.7: Masked image 1 and masked image 2 shows only outer part of MRI brain image.

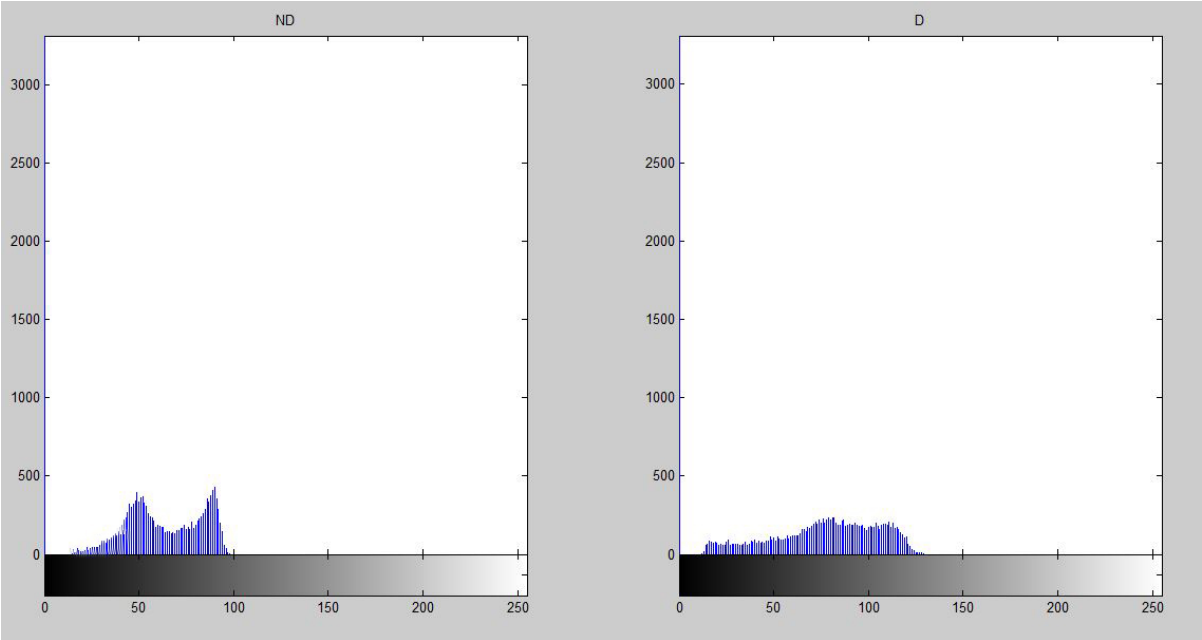


Figure 5.8: Histograms of masked image 1(Right) and masked image 2 (Left).

5.2 Result of Bottom Hat Operation

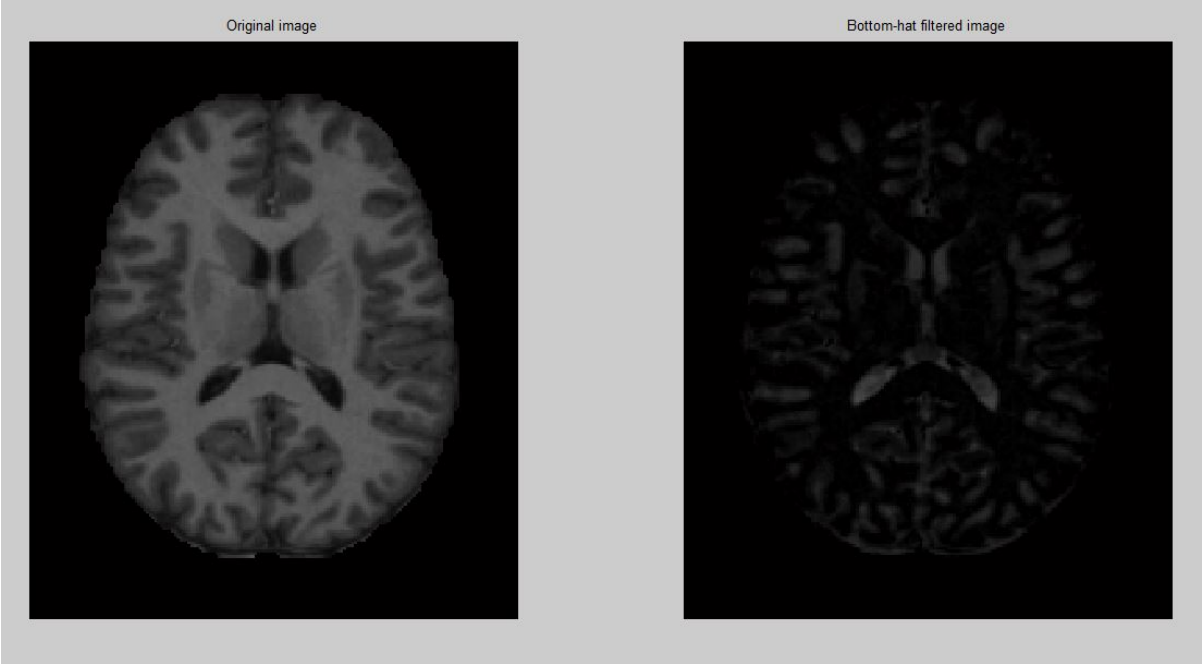


Figure 5.9: Bottom Hat result of normal subject.

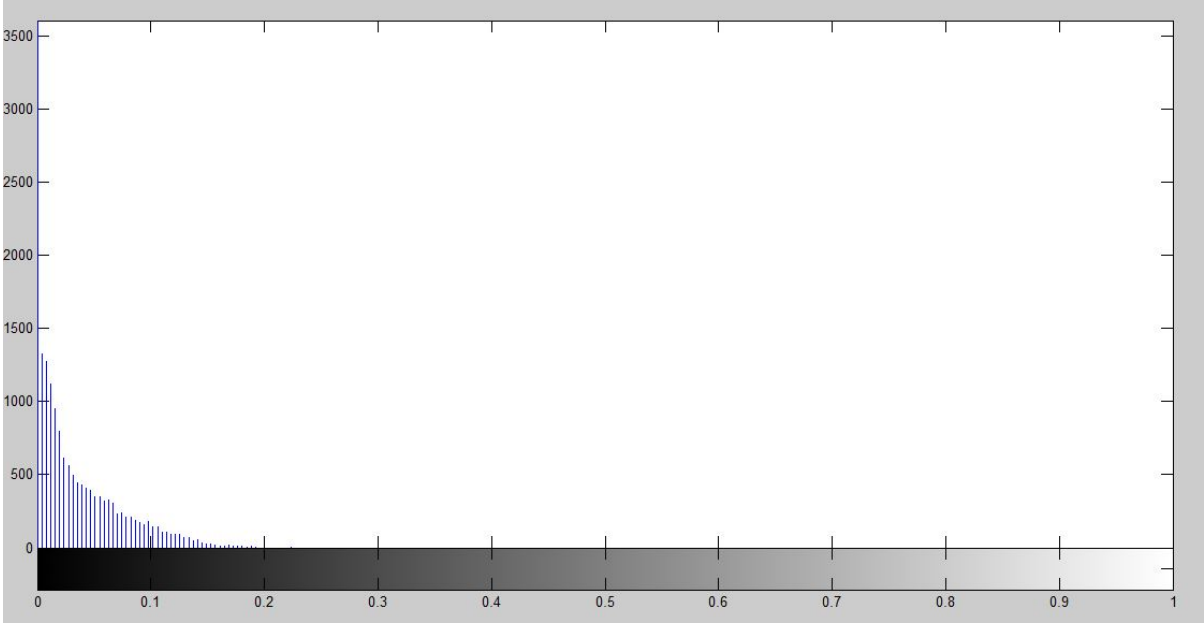


Figure 5.10: Histogram of Bottom hat filtered image.

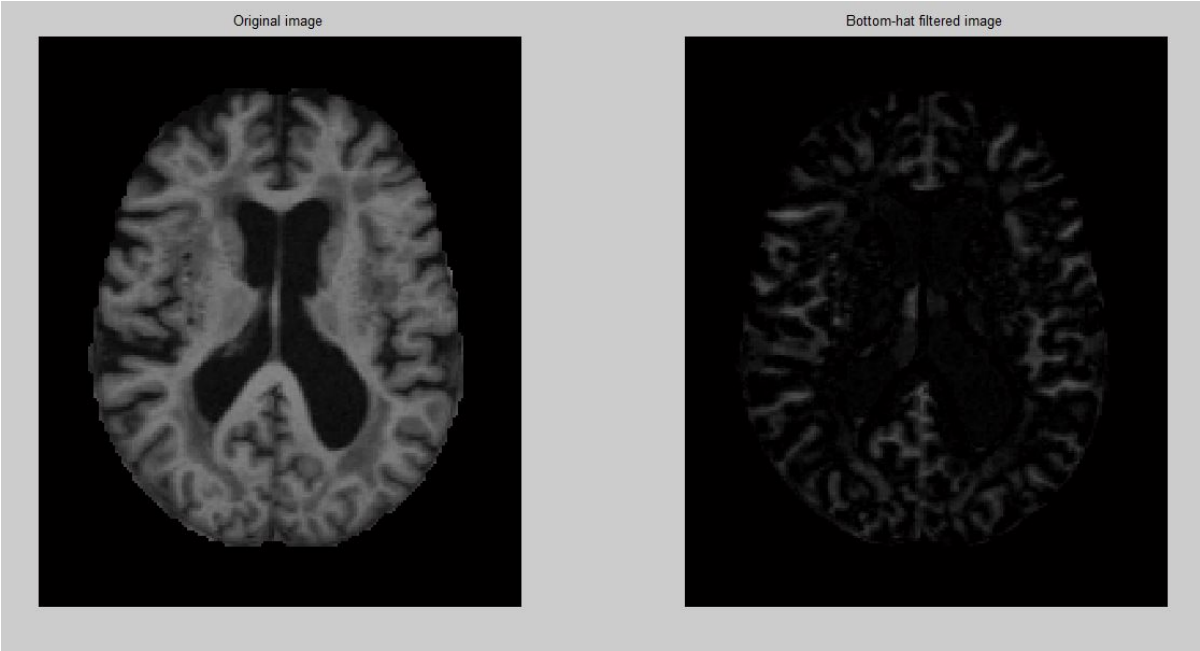


Figure 5.11: Bottom Hat result of AD control Subject.

If we closely observe both results obtained after Bottom hat operation. We found that all the white region present in this case. Not all the Black region is converted in to white. In Fig a we observed that the central section original image is Black, and the resultant image after performing Bottom Hat operation still have the same black region but the other part of MRI brain image except that central section have small sections of Black region distributed all over the image, is converted in to White. That means all the white part of MRI image is converted into Black but the vice-versa is not true.

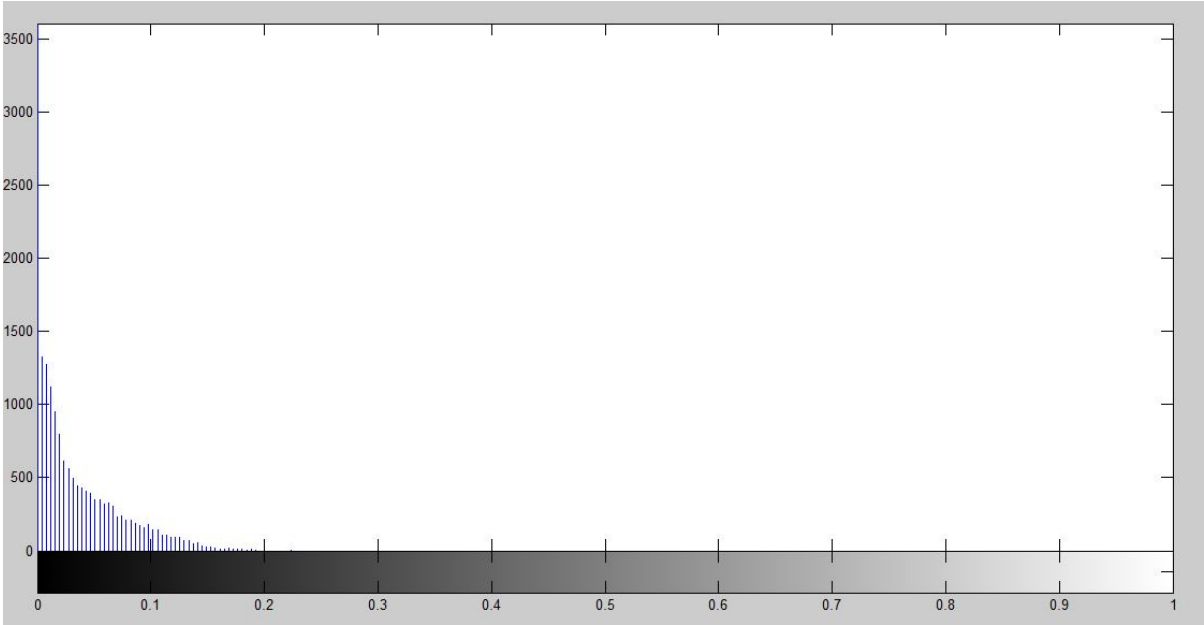


Figure 5.12: Histogram of bottom hat filtered image.

When we compare the histograms of both the bottom hat filtered images. We observe that the more number of black pixels is still present in the diseased MRI image. As shown in fig , the density of intensity level varies from 0 to 0.3 in case of diseased MRI brain image. And it varies from 0 to 0.2 in case of Non-diseased.

5.3 Performance of MFNN classifier

MFNN classifier used so many different parameters to evaluate the training performance. Some of the parameters are Number of iterations, hidden neurons, moment factor, learning rate.

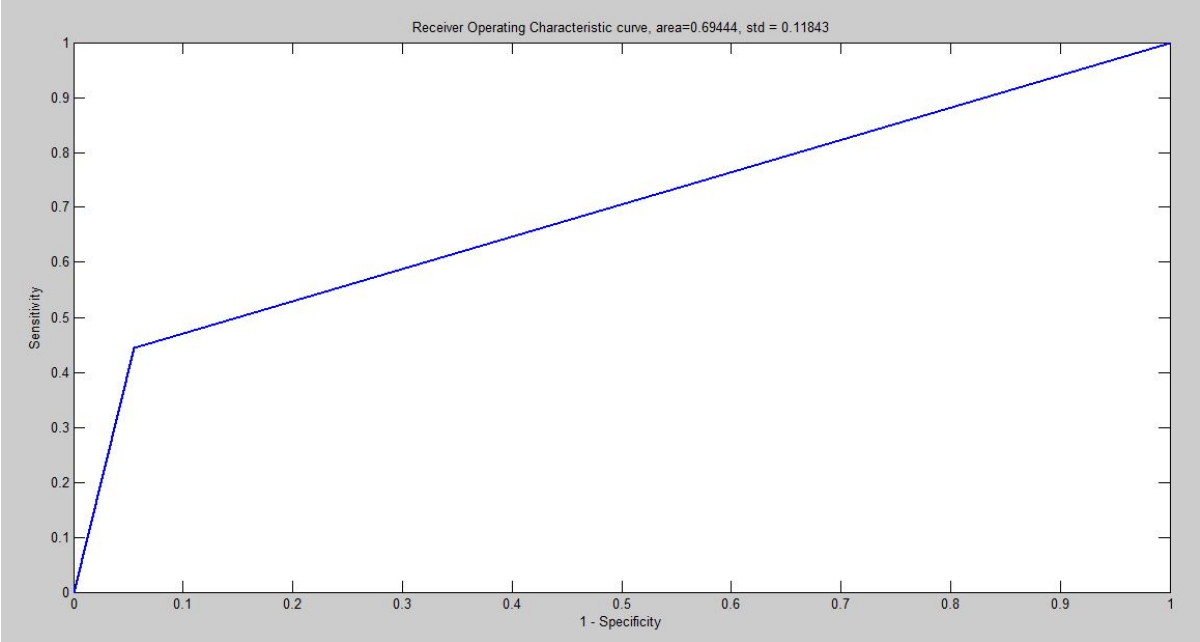


Figure 5.13: ROC curve of MFNN classifier.

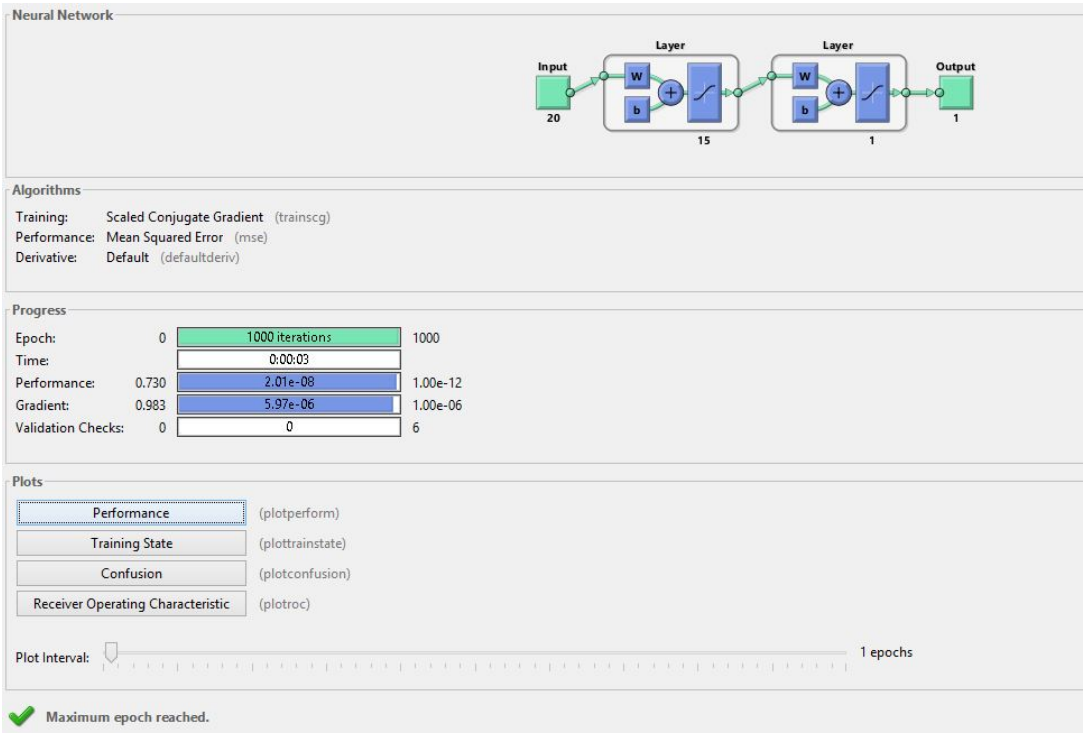


Figure 5.14: NN showing no of iteration, elapsed time and performance.

Fig.5.14 shows the ROC (Receiver operating chractorstic curve) of MFNN classifier. It

also indicates the area under the curve which decides the perfomance of the clsiffiers. When we compare the areas under ROCs of bothe classifiers, we get the larger area under the ROC of SVM classifier because ROC curve follwed the ramp function due to which area increases rapidly as shown in Fig.5.16. But in case of MFNN, there is a rapid change in slope of ROC curve which results decrement in slope, due to which the area under the ROC curve decreases as shown in Fig. 5.14.

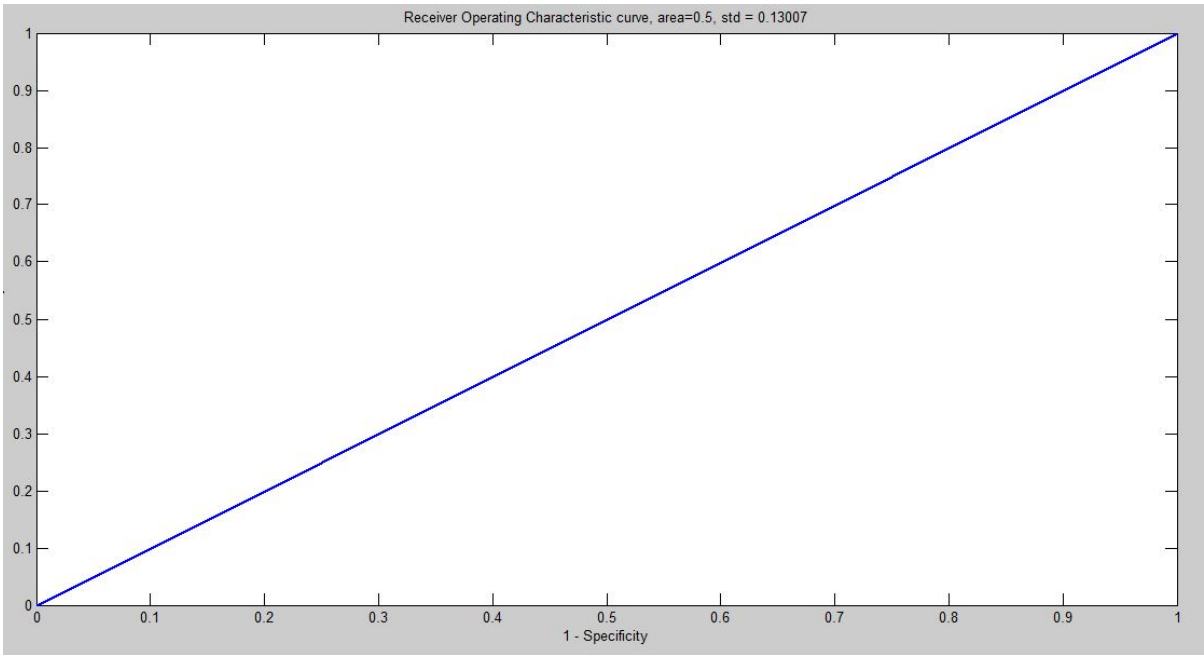


Figure 5.15: ROC curve of SVM classifier.

Chapter 6

Conclusion

Chapter 6

Conclusion

6.1 Conclusion

We have demonstrated a fully automatic method based on pattern recognition and Machine Learning techniques coupled with ANN and SVM for the analysis of MRI data set. That is very helpful in discriminating among AD and healthy controlled subjects. The proposed model produced some comparable results with other relevant works. It was found that SVM classifier produced 91.23% CR whereas ANN produced only 82 % CR. ANN were very less accurate when it was compared with SVM and LS-SVM. When we compared the CR, sensitivity, specificity and area under the ROC curve generated by these classifiers, we saw that both SVM and LS-SVM produced comparable results. The SVM model can successfully classify the AD controlled and normal controlled subjects.

Chapter 7

References

Chapter 7

References

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